REMARKS

By Office Action dated November 6, 2002, Paper No. 10, no claims were allowed. Claims 1-8, 22-24 and 29-30 are pending and under examination.

In conformity with proposed U.S. Patent and Trademark Office rules set forth in OG Notice 25 February 2003, Applicants have included a complete detailed listing of the claims under the section, "Amendments to the Claims." The detailed listing presents all claims that are, or were, in the application. The current amendments to the claims are expressed in the listing. The requirement to provide two versions of a replacement paragraph, section, or claim (a clean version and a marked up version), as set forth in current 37 C.F.R. § 1.121, is waived per the cited OG Notice.

For the sake of clarity, the rejections and objections of the presently outstanding Office Action, Paper No. 10, 11/6/02, are set forth below, in the order in which they were presented and are herein addressed:

1. Claims 1-8, 22-24, 29 and 30 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.
2. Claims 1-8, 22-23, 29 and 30 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not enabled by the specification.
3. Claims 22-24, 29 and 30 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not supported by the specification

INTRODUCTION

The present application was filed 8/31/00, claiming priority from Provisional Patent Application 60/151,766 filed 8/31/99. In Office Action dated 10/2/01, claims 1-8 were rejected under 35 U.S.C. 112 for lack of enablement. That Office Action stated, "The specification does not disclose whether a mutated form of the dystroglycan gene results in cancer, it only discloses many tumor cells do not have normal α-dystroglycan on the surface and thus lack dystroglycan function. Additionally, it does not define dystroglycan function beyond its ability to bind

laminin and there is no record in the art teaching dystroglycan as a tumor suppressor....In addition, the specification does not provide guidance as to what level of alpha dystroglycan would constitute abnormal levels and how these levels would be indicative of potential tumorigenicity." (Office Action mailed 10/2/01, Paper No. 5, p. 5).

In response, Applicants pointed out, in Response (Paper No. 6, dated 1/3/02), that the prior art did show that, although dystroglycan was not known in the art to be a tumor suppressor, dystroglycan was known to be involved in regulation of cell growth and cytoskeletal architecture. Furthermore, the demonstration of a genetic mutation is not necessary to the practice of the present invention. The Specification describes proteolytic cleavage of the dystroglycan and the tumorigenetic results. Paper No. 6 further points to support in the Specification for comparison of ratios of α- to β-dystroglycan (p. 20), for the amount of α-dystroglycan shed (p. 10, ¶ 1 of the Specification), and for evidence of that measurement of α-dystroglycan is indicative of potential tumorigenicity (pp. 24-25 of the Specification).

By Office Action dated 4/23/02, Paper No. 7, the rejection of claims 1-8 under 35 U.S.C. 112, first paragraph was withdrawn. Rejection under 35 U.S.C. 103 over Matsumura et al. (1993) was maintained and a rejection under 35 U.S.C. 102 over Matsumura (1997) was entered. It was the position of the Office at that time that the practice of the presently claimed invention, rather than requiring undue experimentation, would be obvious.

By Response dated 8/15/02, Applicants amended claim 22; added 2 dependent claims (29 and 30); and traversed the obviousness and anticipation rejections.

The present Office Action, Paper No. 10, was issued 11/06/02 in response to the 8/15/02 Response. Claims 1-8, 22-24, 29 and 30 were rejected under 35 U.S.C. 112. Four rejections are made for indefiniteness, as well as one rejection for lack of enablement and one rejection for lack of written description. These are addressed in turn below.

Applicants assume that the rejections of Claims 1-8, as allegedly being anticipated under 35 U.S.C. § 102(b) by Matsumura, et al (1997) and Claims 22-24 as allegedly obvious in view of Coico, et al. and Matsumura, et al (1993) are withdrawn because the Office Action, Paper No. 10

mailed 11/6/02, does not address these rejections. Applicants respectfully request to be advised if any such rejections remain.

I. THE CLAIMS ARE NOT INDEFINITE.

A. Response to Rejection I (a)

The Office Action (Paper No. 10, 11/6/02) alleges that "Claims 1 and 5 recite 'potential tumorigenicity' but it is not clear what the metes and bounds are for the phrase." (page 3, ¶ 2).

Claims 1 and 5 are not indefinite because the specification describes what "potential tumorigenicity" means. The definition of tumorigenicity is found at page 4, paragraph 3 of the Specification, which recites, "This characteristic is referred to as "tumorigenicity," which means the properties of a cell normally associated with tumor forming properties, especially growth arresting properties, normal cell arrest, and appearance in the 3D-BM assay."

The Specification further explains that "[l]oss of a tumor suppressor function, like that of dystroglycan, facilitates the development of tumors, therefore, cells lacking a tumor suppressor are said to have a higher "potential tumorigenicity." In some cases, loss of a single tumor suppressor, like dystroglycan, can indicate a tumorigenic state, and in other cases additional changes to the cell are required before it becomes capable of forming tumors. For the purpose of this application, either case is described as a high potential tumorigenicity." (page 5 of Specification, beginning at line 4).

Furthermore, the art recognizes the above definition, as evidenced by, for example, Murakami, "Functional Cloning of a Tumor Supressor Gene, TSLC1, in Human Non-small cell Lung Cancer," *Oncogene* 21:6936-6948 (2002). A copy of this reference is enclosed as Exhibit A. Murakami relates that "[t]umorigenicity in nude mice has been recognized as the most reliable indicator of malignant features in cancer cells (Fogh et al., 1977). In fact it would represent a relatively common cascade of human tumorigenesis... " (Murakami, p. 6945, Col. 1). Murakami cites Fogh J, Fogh JM and Orfeo T (1977) *J. Natl. Cancer Inst.*, 59, 221-226, a copy of which is also enclosed as Exhibit B. In Exhibit B, Fogh et al. report the tumor-producing

capacity of 127 cancer cell lines by observing how long before these cell lines produced tumors in nude mice. Thus, Murakami's use of the term, "tumorigenicity," is in agreement with the definition of "potential tumorigenicity" provided by the Specification as recited above. Thus, Applicants assert that the terms "tumorigenicity" and "potential tumorigenicity," as defined by the Specification and used in the claims, have been used in the art such that a person having ordinary skill in the art would understand what these terms mean. That is, the terms may be used interchangeably in reference to the malignant phenotype exhibited by the cell and the overall process of cell normalcy to cancerous cell.

The Applicants direct the Examiner's attention to Table 5 of Exhibit A (Murakami, p. 6945) wherein Murakami shows the correlation between select cancer cell lines, their corresponding tumorigenicity and the absence or the amount present of the tumor suppressor gene of interest in those cell lines. In the Specification, the inventors correlated the absence or the amount present of the shed α-dystroglycan fragment in the medium surrounding cells to tumorigenicity as well. Therefore, because others in the art define, demonstrate and correlate tumorigenicity as the inventors have described in the Specification, Applicants assert that the term "potential tumorigenicity" has the requisite definiteness to render clear what assays come within the claims, and the rejection of claims 1 and 5 for indefiniteness should be withdrawn.

B. Response to Rejection I (b).

In Paper No. 10, page 2, ¶ 5, the Examiner alleges that "Claim 1 recites 'medium surrounding cells' but it is not clear what the metes and bounds are for the phrase. Claim 4 indicates that one example of the phrase is blood."

The term "medium surrounding the cells" is clear from the Specification. For examples, page 5, ¶ 3, line 17 of the Specification recites: "[t]he present assays may be carried out on tissue samples, the cells themselves, or on the surrounding medium. *In vivo*, the surrounding medium will comprise the blood and its serum." Page 11, ¶ 2 recites: "To test these possibilities we looked for the presence of α-dystroglycan in the culture medium of cells which shed the protein and asked if it was proteolytically cleaved."

In further evidence, page 14, ¶ 2 of the Specification also recites: "Any assay that detects α-dystroglycan proteolysis would be an assay for the detection of tissue re-organization and cell growth. Assays have been created to test for α-dystroglycan proteolysis in cultured cells, tissue sections, and in blood serum. Assays in cell culture include detection of shed α-dystroglycan fragments in the culture medium, and measurement of the ratio of α-dystroglycan to β-dystroglycan on the cell surface. Assays in tissue samples include detection of proteolysed α-dystroglycan fragments by immunoblotting extracted tissues, or immunostaining of 'nouveau antigens' created by dystroglycan proteolysis. Assays in blood serum include immunologic detection of dystroglycan fragments or nouveau antigens in serum samples."

Other examples of the clear meaning of the term "medium surrounding the cells" may be found at page 17, ¶ 3, line 16 and other places in the specification. In addition, claim 1 has been amended to clarify that the assay of that method is carried out specifically on "medium surrounding cells." Other assays, e.g. claim 5, (which is not encompassed by this rejection) are carried out particularly on cells. Furthermore, Applicants assert that the phrase "medium surrounding the cells" is so commonplace in the art as to be virtually self-explanatory. Accordingly, Applicants request that this rejection be withdrawn because as the metes and bounds of the term "medium surrounding the cells" is adequately defined in the specification and in the art.

C. Response to Rejection I (c)

The Office Action alleges "Claims 1-8 are confusing, therefore indefinite because it is not clear what is being claimed.... The claims could be interpreted as drawn to a cancer screening method by detecting the proteolytic fragment. The claims, as written, could also be interpreted as **a research proposal** of assessing if the 120-130 kD α-dystroglycan fragment could be used as a biomarker for either presence of cancer or antecedent marker for cancer... [T]he examiner will assume that the claims are drawn to tumor screening method using the proteolytic fragments of α-dystroglycan as a biomarker..." (Paper No. 10, mailed 11/06/02, page 2, ¶ 6). Claims 22-24, 29 and 30 are similarly rejected.

Applicants respectfully assert that the method of claim 1 is as the preamble states – " a method for measuring potential tumorigenicity of mammalian cells." Applicants do not understand the Office Action's assertion that this method is an invitation to research or a research proposal. The research necessary to enable the claimed method has already been done and is described in the present specification.

The present specification demonstrates experimentally that a tumorigenic cell line sheds into the supernatant a previously unknown fragment of α-dystroglycan, having an Mr of 120-130kD. This is demonstrated in Fig. 1, which shows an SCg6 mammary carcinoma cell supernatant having a distinct band in the 120-130kD region. This band is significantly reduced when protease inhibitors are added to the cell culture. See page 5, ¶ 2 – p. 6, ¶ 2 of the Specification. As explained there, one may use a direct cell medium assay (using the disclosed antibody IIH6 on p. 16 of the Specification) or use a cellular assay. In the latter case, quantification is provided by use of an assay of α-dystroglycan to β-dystroglycan. In other words, there is a clear correlation between the dystroglycan on the cell surface and the proteolytic fragment in the cell medium.

Taking the next step, the specification next teaches that the degree to which the α-dystroglycan on a cell surface has been cleaved and shed into the medium correlates with the tumorigenicity of the cell. In Fig. 2, it is shown that 5 of 8 tumor cell lines tested lacked detectable cell surface α-dystroglycan. It follows that the above described fragment of Mr 120-130 kD is present in the cell medium. Furthermore, Fig. 1A shows that the fragment of 120-130 kD may be detected in the medium even when there is still some detectible amount of α-dystroglycan remaining on the cell surface.

In conclusion, the claimed method is not an invitation to a research proposal. It recites a method for detecting a certain polypeptide, said method having utility in evaluating the tumorigenic potential of a mammalian cell population.

II. THE CLAIMS ARE ENABLED.

Applicants now address the rejection by the Office Action of claims 1-8, 22-24, 29 and 30 under 35 U.S.C. 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are interpreted as a method of assessing cancer risk using the proteolytic α-dystroglycan fragments. See rejection of claims 1-8 above." (Office Action, Paper No. 10, 11/6/02, page 3, ¶ 3).

A. Response to Rejection II (a)

After reciting what the figures show, the rejection continues, "[o]ne cannot extrapolate the teachings of the specification to the claimed invention because the specification provides neither guidance on nor exemplification of how to correlate the data presented in the specification with the ability to use α-DG fragments for the assessment of cancer risk. " (Office Action, Paper No. 10, 11/6/02, page 4, ¶ 1).

Applicants respectfully disagree and submit that the specification provides guidance on how to correlate the data presented in the specification with the ability to use α-dystroglycan fragments for the assessment of cancer risk. The specification exemplifies an assay for detecting a 120-130 kD fragment of α-dystroglycan from eight different mammalian cell lines. While the examples use immunoblotting, it is well within ordinary skill in the art to use other immunological assay techniques and to use other cells. While the exact calibration curves to be used in the assay are not set forth, it is a mere matter of routine experimentation to establish the appropriate standards and controls for a useful assay. It is clear that the 120-130 kD fragment is circulating in the cell medium, and that is the subject matter being claimed. It is irrelevant what other fragments may also be circulating or whether the fragment is at some point degraded. The fragment is detectible, can be detected, and was detected.

It is also to be noted that the leading case on enablement, *In re Wands*, 8 USPQ2d 1400 (1988), discussed at MPEP 2164.01, involved an immunoassay and found that the level of skill in this art was very high. Therefore, Applicants request that the rejection be withdrawn because

the specification enables an ordinary person skilled in the relevant art to use the 120-130 kD α-dystroglycan fragments for the assessment of cancer risk.

B. Response to Rejection II (b)

The rejection further continues, "Further, it is not clear whether the antibody disclosed in the instant application could be used to detect the fragment(s) circulating in blood if the fragments are further degraded." (Office Action, Paper No. 10, 11/6/02, page 4, ¶ 1, line 8).

As stated in connection with Response II (a), the antibody disclosed in the instant application was in fact used to detect the fragments, albeit in cell culture medium. In this case, the *in vitro* system is an art recognized model for *in vivo* behavior. The disclosure is therefore enabling in accordance with MPEP 2164.02. See enclosed "Declaration of Judith Campisi, Ph.D."

C. Response to Rejection II (c)

The Office Action rejection further continues, "The specification does not teach if some normal cells *in vivo* secrete the fragments for yet unknown functions." (Paper No. 10, 11/6/02, page 4, ¶ 10).

The specification teaches that shedding occurs to a very low degree in normal cells. See paragraph bridging pp 15-16 of the Specification, where it is stated, "The ratio of α-dystroglycan to β-dystroglycan is higher in the BT474 [less aggressive tumor] cell line, Figure 2, lane 2, than any other cell line or in normal cells, suggesting that some degree of shedding occurs in all cells, but that shedding is low or absent in BT474s."

The thrust of the work described in the specification is that normal cell organization involves dystroglycan binding of normal cells, so it is expected that the degree of shedding (proteolysis) correlates with tumorigenicity.

D. Response to Rejection II (d)

The rejection further continues, "Further, the specification does not teach what kinds of tumor growth could be correlated with the detection of the fragments in blood. In short, the specification does not present any *in vivo* data to correlate either detection of the fragment in

blood or absence of the fragment on cell surface to growth of any tumor." (Office Action, Paper No. 10, 11/6/02, page 4, ¶ 1, line 15). The Office Action then outlines the Tockman *et al.* reference that discusses the requirements to validate an assay (*Ibid*, line 19).

The specification teaches that shedding correlates to aggressiveness of the cancer cell lines. See the bottom paragraph of p. 15 of the Specification, where it is stated, "Immunoblots showed that the β-dystroglycan subunit was present in all breast tumor cell lines tested, but that the α-dystroglycan subunit, which binds laminin, was greatly diminished or absent in 5 of 8 (Fig. 2). Evidently the α-dystroglycan subunit was shed from the cell surface. Loss of α-dystroglycan in these cell lines correlated with loss of organization in the 3D BM assay and correlated with more aggressive tumor cell behavior *in vivo*."

For a discussion of the issue of *in vitro* versus *in vivo* data, see Response II(e) immediately below.

E. Response to Rejection II (e)

The Office Action alleges, "[f]urther, one cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach that method of positively correlating tumor cell growth *in vivo* to either detection of the smaller fragment shedding into blood, or to absence of the smaller fragment on cell surface. The *in vitro* demonstration of restoring normal phenotype of cancer cells with the protease inhibitor or with overexpression of human dystroglycan cannot be correlated to the invention as claimed, because the characteristics of cultured cell lines generally differ significantly from the characteristics of in vivo primary cancers or metastatic cancers." (Paper No. 10, 11/6/02, page 5, ¶ 1).

The Office Action (Paper No. 10, 11/6/02) further alleges on page 6, ¶ 1, "[t]he specification provides insufficient guidance, and provides no working examples of correlating in vivo tumor growth to either detection of 120-130 kDa (or 60 kDa) fragments of alpha-dystroglycan or to absence of the fragment on the cell surface, which would provide guidance to one skilled in the art to use the claimed invention without undue experimentation. Considering

lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention."

This rejection is based on the argument that results in cultured cell lines *in vitro* cannot be extrapolated to *in vivo* conditions.

As stated in MPEP 2164.04,

> In order to make a[n enablement] rejection, the examiner has the initial burden to **establish a reasonable basis to question the enablement** provided for the claimed invention. *In re Wright*, 999 F.2d 1557, sought to 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, **unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support**. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370. (emphasis supplied in bold).

The experimental work described in the specification provides a reasonable expectation of success in determining tumorigenic potential. The Specification states, "Because α- and β-dystroglycan are translated as a single polypeptide, it was surprising that α-dystroglycan was not detected on the cell surface of many cells when β-dystroglycan was present. We concluded that, by some mechanism, α-dystroglycan was being shed from the cell surface" (p. 11, ¶ 1). "We believe α-dystroglycan shedding occurs principally in cells that are reorganizing and growing. Little of such activity occurs in adult tissues, except in cases like the normal processes of mammary gland development, and perhaps angiogenesis. However, such activity would occur on a large scale during hyperplasia or tumor cell growth and the accompanying angiogenesis. α-

dystroglycan is shed in two forms, one which binds laminin and a smaller portion with no known binding activity. An assay that detects α-dystroglycan proteolysis would be an assay for the detection of tissue re-organization and cell growth." (p. 13-14 of the Specification).

The Office Action has provided detailed argument and references regarding the unpredictability of the present art. The Tockman *et al.* reference describes the validation of cancer markers against known clinical end points. The Freshney reference is cited, as well as the Dermer reference. The essence of these references is that cell culture results can never be sufficient to enable an assay to be used on samples taken *in vivo*. The Examiner is in effect requiring that an animal experiment be done with cells of various tumorigenic potential, that various measurements of α-dystroglycan and α-dystroglycan fragments of 120-130 kD be made on samples taken *in vivo*, and a demonstration that the results positively correlate with tumorigenic potential.

However, such experiments are not required. They were not required in the publication arising from this work and are not required to meet 35 U.S.C. 112. In fact, in accordance with MPEP 2164.02, no working examples are required. As stated there,

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications).
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> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an

invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted).

Furthermore, this is not a case where there is justification to disbelieve the assertions made in the present application. MPEP 2164.04 provides that the teachings of the specification as to enablement must be taken by the Examiner as true "unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." The Tockman *et al.*, Dermer and Freshny references were apparently provided in the Office Action to show that the enablement specifically taught as based on the working examples provided is to be doubted in this case.

Applicants assert that the Specification does enable one with skill in the art to positively correlate the shedding of α-dystroglycan with *in vivo* tumor cell growth. The Specification provides Example 5 which shows that restoration of dystroglycan function restores normal cell behavior to tumor cells (p. 24-25 of the Specification). Over-expression of the human dystroglycan gene within the tumorigenic cell line HMT-3522-T4 restored normal cell phenotype causing cells to arrest growth and form organized acinar structures. But not only did the over-expression of dystroglycan in formerly tumorigenic cells control tumor growth *in vitro*, "[i]n addition to reverting the tumorigenic phenotype in culture assays, the cells possessing restored dystroglycan function did not produce tumors after subcutaneous injection into the flanks of nude mice (5×10^6 cells/injection), whereas the control cells [that did not over-express dystroglycan] did. These results reveal the role of dystroglycan as an important suppressor of tumorigenicity in cells." (p. 25, line 16 of Specification).

Furthermore, there are other publications that may be cited to support Applicant's position that the presently claimed assay does correlate with potential *in vivo* tumorigenicity. For example, Muschler et al. "A Role for Dystroglycan in Epithelial Polarization: Loss of Function in Breast Tumor Cells," *Cancer Research* 62:7102-7109 (Dec. 2001) present evidence

that the levels of α-dystroglycan present on the cell surface correlates strongly with tumorigenicity in the nude mouse model. Henry et al., *Hum Pathol* 32:791-795 (2001) describe the correlation between dystroglycan expression and more high grade breast and prostate cancers. Sgambato et al., *Am. J. Path.* 152:849-860 (2003) describe the positive correlation between dystroglycan expression and survival rates in breast and colon cancers. These references are attached herein as Exhibits C, D, and E, respectively.

Thus, it is submitted that the present Specification provides the requisite reasonable correlation between the working examples and the claimed method.

III. THE CLAIMS ARE SUPPORTED.

The Office Action of 11/6/02 (Paper No. 10) alleges on p. 6, ¶ 2, that "[c]laim[s] 22-24, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amended claims are drawn to an assay method of positively correlating detection of alpha-dystroglycan fragments in blood to tumor growth. This examiner is unable to find support for this positive correlation assay method in the originally filed specification. Applicant is requested to point (to) support for the amendment."

The Specification contains numerous specific references to such a method, in addition to the specific examples where assays of α-dystroglycan fragments are carried out as claimed in the method of claim 22 (once amended) which recites that α-dystroglycan fragments bound to a labeled antibody are positively correlated with tumor cell growth. Applicants point the Examiner to the following passages in the Specification.

On page 6, ¶ 1, it is stated, "Identifying the presence of the α-dystroglycan fragment indicates a higher potential tumorigenicity." The third paragraph states, "A correlation between tumorgenicity and the loss of α-dystroglycan through proteolysis has been shown."

At page 7, ¶ 2, the Specification describes an assay of proteolysed α-dystroglycan fragment in blood serum and states "[t]his assay would add a labeled antibody specific for an α-dystroglycan or a fragment thereof , and assaying for the amount of bound label present in the serum."

On p. 10, in the first paragraph continued from p. 9, the Specification describes the correlation between the presence of α-dystroglycan and tumorigenic behavior in the art-recognized model of the 3D basement membrane model. The Specification also shows that tumor cells having the dystroglycan function restored, when injected into nude mice, demonstrate a reversion of tumorigenic phenotype (p. 10, last paragraph and Example 5 on p.24-25). Quantification of the dystroglycan fragment is again discussed in Example 1 of the Specification (p.18, ¶ 1).

In conclusion, Applicants assert that the methods recited in independent claim 22 (previously amended) and the claims dependent thereon are specifically described as required by 35 U.S.C. 112, first paragraph and respectfully request that the rejection be withdrawn.

CONCLUSION

In the presently outstanding Office Action, it appears that Applicants are not only being limited to the assay contained within the four corners of the specification, but to the work actually exemplified in the figures and examples. Applicants submit that there are significant other aspects of the present teachings that must be considered in determining compliance with 35 U.S.C. 112. In particular, a teaching has been provided which enables one of ordinary skill in the art to make and use the claimed assay. It is not necessary that the specification provide all of the data needed for an FDA submission or an investigational device exception. It is not necessary that the specification provide extensive *in vivo* population or clinical studies in order to meet the enablement/utility standards of 35 U.S.C. 101. All that is required is that "undue experimentation" not be required in order for the claimed method to be useful. Any "specific, substantial and credible use" within the claimed scope is acceptable. Applicants request

consideration of the scientific opinions expressed in the accompanying Declaration of Judith Campisi, Ph.D. The Declaration serves to remove apparent doubt of the Examiner as to the truth of the statements in the Specification.

Applicants submit that the claims under examination are not indefinite and are enabled and supported by the specification. No new matter has been introduced by the amendments. Applicants urge the Examiner to withdraw all rejections. Applicants believe that, as amended, claims 1-8, 22-24, and 29-30 are in condition for allowance, and such action, as well as the prompt issuance of the present case, is earnestly solicited.

Applicants also request the Examiner to consider the enclosed references, Exhibits A-E, as relating to this Amendment and request the present Amendment be entered into the record as references cited.

Applicants hereby request a three month extension of time from February 6, 2003 to May 6, 2003. A Petition for Extension of Time under 37 C.F.R. § 1.136(a) is included herewith in duplicate. The Office is authorized to charge $465, and any necessary and additional fees that may be due, to Deposit Account No. 12-0690.

For the reasons set forth above, Applicants respectfully request that a timely Notice of Allowance be issued in this case. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned at (510) 495-2839.

Respectfully submitted,

Dated 5/2/03

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